American Journal of Respiratory and Critical Care Medicine/AJRCCM

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Journal:	*American Journal of Respiratory and Critical Care Medicine*
Manuscript ID:	Blue-201105-0848OC.R3
Manuscript Type:	OC - Original Contribution
Date Submitted by the Author:	01-Nov-2011
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Keywords:	Pulmonary hypertension, Heart rate recovery, Six minute walk test, Clinical worsening

Heart Rate Recovery Predicts Clinical Worsening in Patients with Pulmonary Arterial Hypertension

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Brief title: Heart rate recovery in pulmonary hypertension

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Descriptor:

9.35 Pulmonary Hypertension: Clinical-Diagnosis/Pathogenesis/Outcome

Manuscript word count: 3171

Conflict of interest:

Omar A. Minai is a member of the SAB and Speakers Bureau for Actelion, Gilead, United Therapeutics, and Pfizer and a member of the SAB for Bayer.

None of the other authors have any relevant conflicts of interest.

Grant statement:

This study was not supported by any grants.

At a Glance Summary

Scientific Knowledge on the Subject:

Six-minute walk distance (6MWD) has been shown to be a predictor of survival in patients with idiopathic pulmonary arterial hypertension (IPAH). Due to rapid disease progression, time to clinical worsening has been used as an end-point in several trials in patients with IPAH. Accurate indicators of long-term prognosis are key measures of outcome for patients with any disease, especially one where patients are likely to deteriorate despite therapy. Recent publications in the field of pulmonary hypertension have focused on complicated risk scores to predict long-term outcomes. Several factors such as expense, time, and limited resources limit widespread clinical use of these risk scores since they require several points of data. Cheap and easily measured biomarkers that can predict clinical worsening are needed in patients with IPAH.

What This Study Adds to the Field:

This study shows that heart rate recovery at 1 minute after six-minute walk test is an easily measured biomarker that is highly predictive of clinical worsening and time to clinical worsening in patients with IPAH. We also show that the addition of heart rate recovery at 1 minute to 6MWD increases the capacity of 6MWD to predict clinical worsening in patients with IPAH. Given its predictive ability, ease of measurement, no cost, and widespread availability we believe that this will represent an important advance in the care of these patients.

Abstract:

Rationale: Reduced heart rate recovery after exercise is associated with increased mortality in cardio-pulmonary diseases.

Objectives: We sought to evaluate the association between heart rate recovery at one minute of rest (HRR1) after 6-minute walk test (6MW test) and clinical worsening in patients with idiopathic pulmonary arterial hypertension (IPAH).

Methods: HRR1 was defined as the difference in heart rate at the end of 6MW test and at one minute after completion of the 6MW test. Between August 1, 2009 and March 30, 2010, 75 consecutive patients with IPAH underwent 6MW test and were included in the analysis.

Results: Compared to patients with HRR1≥16 [N=45(60%)], those with HRR1<16 [N=30(40%)] were more likely to have clinical worsening (odds ratio 9.7; 95% confidence interval [CI], 3 to 30; p <0.001) and shorter time to first clinical worsening event (TCW) (6.7 months versus 13 months; p<0.001) during follow-up. By multivariable analysis the best predictors of clinical worsening were HRR1 <16 (HR 5.2; 95% CI, 1.8 to 14.8; p=0.002) and mPAP (HR 1.04; 95% CI, 1.007 to 1.08; p=0.02). Compared to 6MWD, HRR1 <16 was a better predictor of clinical worsening (c-statistic 0.757 vs. 0.703) and TCW (c-index 0.730 vs. 0.696). The addition of HRR1 increased the ability of 6MWD to predict clinical worsening events.

Conclusions: HRR1 after 6 MW test is a strong predictor of clinical worsening and TCW in patients with IPAH. The addition of HRR1 to 6MWD increases the capacity of 6MWD to predict clinical worsening and TCW in patients with IPAH.

Abstract word count: 250

Key Words:

Pulmonary hypertension

Heart rate

Six minute walk

Survival

Clinical worsening

Introduction:

Pulmonary arterial hypertension is a disorder that is rapidly progressive and prognosis remains poor despite recent advances in therapy (1). Several investigators have identified prognostic variables (2-4), however, their reproducibility and clinical relevance to patients on specific vasoactive therapy remains in question. The REVEAL Registry has identified factors (5) that may be employed to predict long-term outcomes in these patients. Although these may be of value, their ease-of-use in everyday practice in the community setting is unclear. In addition, disease heterogeneity makes accurate survival predictions more prone to error.

Pulmonary hypertension limits functional capacity and poor functional capacity has been consistently found to be an indicator of poor prognosis in patients with idiopathic pulmonary arterial hypertension (IPAH) (1,2). Cardiopulmonary exercise testing has been used to predict survival in patients with IPAH (6-8). The distance walked during a standardized six minute walk test (6MWD) (9) has a strong correlation with the cardiopulmonary exercise test (10) and has been shown to be a predictor of survival in IPAH (11). Recent publications have reported on the presence of autonomic dysfunction and its possible association with survival in patients with pulmonary arterial hypertension (12-14). Heart rate recovery refers to the reduction in heart rate with rest after graded exercise (15). Abnormal heart rate recovery during the first minute after graded exercise (HRR1) is a powerful predictor of overall mortality in patients referred for exercise testing (16,17), CHF patients (18), and those with COPD (19) and idiopathic pulmonary fibrosis (20). Heart rate recovery after exertion has not been examined as a prognostic marker in patients with IPAH. The addition of heart rate recovery to the 6MW test may

increase its ability to predict survival and TCW in this population. The main objectives of our study were to determine whether HRR1 was a predictor of clinical worsening and time to clinical worsening (TCW) in patients with IPAH, to define the cutoff value for abnormal HRR1 in patients with IPAH, and to examine the predictors of an abnormal HRR1 in these patients. Some of the results of this study have been previously reported in the form of an abstract (21).

Methods:

The study was approved by our Institutional Review Board. Patients with IPAH evaluated between August 1, 2009, and March 31, 2010, who completed a 6MW test were enrolled. Only patients with baseline right heart catheterization confirming a diagnosis of PAH and without evidence of secondary etiologies of PAH were included.

PFTs were performed according to ATS/ERS criteria (22). At our center, 6MWT is performed according to the ATS/ERS criteria (in terms of instructions to patients) (9); however, the test was modified by recording heart rate at the end of the 6MW test and at one minute after completion of the test with the patient seated. The 6MW test is begun after the patient has been seated for ten minutes. Pulse oximeters (Ohmeda Biox 3740 or Ohmeda 3900; Datex-Ohmeda, Inc; Laurel, MD) with finger probes were used. These oximeters display heart rate and Spo2. Supplemental oxygen flow rates were used according to the subjects' current oxygen prescriptions.

Assessment of HRR and echocardiographic parameters and BNP were performed on the same day and no changes were made between these measurements. Baseline right heart catheterization values were used in all patients and the time interval between the

RHC and the 6MWT was less than 6 months in approximately 50% of the patients. HRR was defined as the difference between a subject's heart rate at the 6th minute of the 6MW test and at one minute after completion of the 6MW test (HRR1). Clinical worsening was defined as any of four different end-points: death, lung transplantation, hospitalization for worsening PH, or escalation of PH therapy (defined as addition of oral therapy or change to or addition of parenteral therapy to existing oral PH therapy). Time to clinical worsening was defined at the time from the date of the 6MW test to the first clinical worsening event as outlined above. Echocardiographic measurements and adjudication of PH hospitalization were performed blindly by physicians unaware of individual results of the 6MWT and HRR.

Like Cole and colleagues (16) and LeBlanc and Crowley (23), we determined the value for abnormal HRR by finding the maximum value of the log-rank chi-square statistic for all possible cutoff points for abnormal HRR between the 10th and 90th percentiles (at one minute of recovery) in the study sample. We identified the cutoff value to be 16 beats at one min after the 6MW test. Continuous measures were described as means, standard deviations, and percentiles and categorical measures were summarized using frequencies and percentages. The two sample T-test or the Wilcoxon rank sum test was used to evaluate the association between HRR1 (binary) and continuous measures and the Pearson's chi-square test or Fisher's exact test was used to assess the association between HRR1 (binary) and categorical measures. For the association involving ordinal measures, Cochran-Armitage trend test was used. Pearson's correlation coefficient was used to assess the correlation between HRR1 (continuous) and continuous measures. We used multivariable logistic regression to identify independent

predictors of abnormal HRR (ie, heart rate dropping by <16 beats at one minute into recovery). For the multi-variable analysis, risk factors with a p-value < 0.05 by univariable analysis, that were felt to be clinically relevant, were considered as candidates in the final model. Proportional hazard survival regression analyses with backward model selection were performed to evaluate the association between the time to clinical worsening and the risk factors; and multi-variable logistic regression with backward model selection was implemented to assess the association between HRR1 (binary) and the risk factors. Receiver Operating Characteristic (ROC) curve analysis via logistic regression was performed to assess the prediction ability of HRR1 and 6MWD to identify clinical worsening. The concordance index (C-index) was used to examine the ability of HRR1 to predict TCW relative to other predictors such as 6MWD and NYHA functional class. All tests were performed at a significance level of 0.05. SAS 9.2 software (SAS Institute, Cary, NC) was used for all analyses.

Results:

Overall characteristics of study population:

Between August 1, 2009 and March 30, 2010, 75 patients with IPAH underwent 6MW test and this group formed the study cohort. Table 1 outlines the clinical and hemodynamic characteristics of the study population. Patients were mostly Caucasian females in World Health Organization functional class (WHO FC) II or III. We found the cut off value for an abnormal HRR1 to be <16 beats.

Patients with HRR1 <16 beats were more likely to have abnormal renal function, have lower FVC % predicted, lower 6MWD (Figure 1), have lower peak and delta HR,

higher BNP, and were more likely to require oxygen supplementation with 6MW test. All patients in WHO FC I had HRR1 ≥16 and all patients in WHO FC IV had HRR1 <16. Patients with HRR1 <16 were also more likely to have right atrial dilation and right ventricular systolic dysfunction on Doppler echocardiography. On baseline right heart catheterization, patients with HRR1 <16 had higher mean right atrial pressure, systolic pulmonary artery pressure, and mean pulmonary artery pressure, and lower mixed venous oxygen saturation compared to patients with HRR1 ≥16. Most patients (N=71) were already on PH specific vasodilator therapy at the time HRR1 was measured, however, all 4 patients not on PH specific therapy were in HRR1 <16 group.

Relationship of HRR1 to clinical worsening events:

Table 2 outlines the association between HRR1 <16 and clinical worsening events. Patients with HRR1 <16 were more likely to have clinical worsening events and had shorter TCW (6.7 months versus 13 months) during follow-up compared to patients with HRR1 ≥16 (Figure 2). Both log-rank and Wilcoxon tests gave a p-value <0.001 for TCW indicating the significant difference in worsening events between the 2 groups (Figure 2). At any time during the follow-up period, the odds of clinical worsening were significantly greater for patients with HRR1 <16 than for patients with HRR1≥16 ([OR], 9.7; 95% CI, 3 to 30; p <0.001). All 4 events, namely death, lung transplantation, hospitalization for PH worsening, and escalation of therapy were more likely to occur in patients with HRR1 <16.

Using the entire study sample, HRR1 <16 was the strongest predictor of clinical worsening by univariable analysis (Table 3). Variables with the lowest p values by univariable analysis were included in the multivariable model and the best predictors of

clinical worsening were HRR1 <16 (HR 5.2; p=0.002) and mPAP (HR 1.04; p=0.02). Re-analysis of our data after excluding patients on beta blockers (N=12) and those who underwent lung transplantation as their worsening event (N=6) still showed that HRR1 <16 was the best predictor of TCW. Excluding those on beta blockers, the median TCW for the HRR1 < 16 group was 8.4 months, and the median TCW for the HRR1 ≥ 16 group was 13.0 months. Both log-rank and wilcoxon test give a p-value of 0.0003, indicating the significant worsening difference between the two groups. Excluding those who underwent lung transplantation, the median TCW for the HRR1 < 16 group was 8.9 months, and the median TCW for the HRR1≥ 16 group was 13.0 months. Both the Log-rank and the Wilcoxon test gave a p-value of < 0.001, indicating the significant worsening differences between the two groups.

HRR <16 also identified a higher proportion of NYHA 2 and NYHA 3 patients with clinical worsening compared to 6MWD <335 and BNP >100 (Table 4). All 3 measures accurately identified all NYHA 4 patients with clinical worsening.

Incremental utility of HRR<16 in predicting clinical worsening and TCW with c-modeling:

By c-statistic, using the logistic regression model, HRR1 <16 was a better predictor of clinical worsening in our study population compared to 6MWD alone (Table 5a). This was true when the analysis was performed using a previously known predictor of poor prognosis of 6MWD <380 meters (11) or when using 6MWD as a continuous variable. The best 6MWD that predicted clinical worsening in our study population was determined to be 335 meters using ROC analysis using the maximum of the sum of the

sensitivity and specificity (AUC 0.653). In this model, HRR1 <16 was a better predictor of clinical worsening (AUC 0.757) and had additive value as a predictor of clinical worsening events over 6MWD <335, 6MWD <380, or 6MWD as a continuous variable alone.

We also performed c-index calculation using Cox proportional regression analysis to assess the incremental ability of HRR<16 to predict TCW. This model (Figure 3 and Table 5b) showed that HRR<16 improved the ability of 6MWD to predict TCW (Figure 3a) and the addition of other parameters did not increase this appreciably (Figure 3b).

Correlates and predictors of HRR1 <16:

Table 6 presents results of logistic regression for predictors of HRR1 <16. By multivariable logistic regression, the best predictors of HRR1 <16 were B-type natriuretic peptide (BNP) and baseline WHO FC. HRR1 had a significant negative correlation with age, renal function, BNP, and mean right atrial pressure and a significant positive correlation with % predicted forced vital capacity, % predicted forced expiratory volume in 1 second, 6MWD, and peak heart rate during 6MW test (online supplement Table 1).

Association of HRR1 <16 with known predictors of poor prognosis in IPAH:

We also sought to determine the association between HRR1 <16 and several known predictors of poor prognosis in patients with IPAH (Table 7). Patients with HRR1 <16 were more likely to require supplemental oxygen during the 6MWT, be in WHO FC 4, have worse WHO FC, have BNP >100 pg/ml, have Na ≤136, and have more severe RV systolic dysfunction and pericardial effusion on Doppler echocardiography.

Discussion:

The most important finding of our study is that HRR1 is an easily measured biomarker that is highly predictive of clinical worsening and TCW in patients with IPAH. Secondly, our results show that the addition of HRR1 to 6MWD increases the capacity of 6MWD to predict clinical worsening and TCW in patients with IPAH. Thirdly, our data showed that compared to 6MWD and BNP >100, HRR <16 could more accurately predict clinical worsening in patients who were less functionally limited. Lastly, we found that HRR1 <16 was highly correlated with several previously published indicators of poor prognosis in patients with IPAH.

The 6MW test is thought to reliably reflect the ability to perform daily activities, in a quantitative manner, in several pulmonary and cardiac diseases. The 6MW test has been shown to be associated with quality of life (24) and survival in patients with IPAH (2,11,25). Change in 6MWD in response to medical therapy has been used as the primary end-point in several large medication trials in patients with PAH (1,25) and researchers have pointed out the strong association between the 6MW test and the cardiopulmonary exercise test (9). More recently, it has been postulated that a composite end-point focused on clinical worsening events may be a more reliable reflection of outcome (2,25). Poor heart rate recovery at 1 (16,17) and 2 (26) minutes have been shown to be important prognostic variables in patients with suspected coronary artery disease referred for cardiopulmonary exercise testing. Poor heart rate recovery has been shown to be an indicator of reduced survival in pulmonary diseases such as chronic obstructive pulmonary disease (19) and idiopathic pulmonary fibrosis (20). This is the first study to

show that poor HRR1 after 6MW test is a strong indicator of clinical worsening and TCW and therefore has important prognostic implications for patients with IPAH.

HRR1 was also a very strong predictor of future escalation of PH therapy in patients already receiving PH specific therapy. Several recent studies have focused on trying to determine baseline predictors of survival in patients with pulmonary arterial hypertension (1,2). Very few have focused on factors that may predict survival or the need for additional therapy in patients already on PH specific therapy (5). Most of our patients were on PH specific therapy and HRR1 <16 accurately predicted need for additional PH therapy as determined by the patients' treating provider. This is an area that requires further study in a prospective cohort. Seven of 10 deaths were in the HRR1 <16 cohort although this difference was not statistically significant likely because of the sample size.

Recent publications have questioned the ability of 6MWD to predict worsening events and survival (27,28). Our data showed that the addition of HRR1 increased the ability of 6MWT to predict clinical worsening and TCW. The addition of HRR1 to 6MWD may therefore improve the predictive ability of the 6MW test. The addition of other easily available parameters such as BNP >100 and NYHA did not change this appreciably. Another important finding in our data was the ability of HRR <16 to more accurately predict clinical worsening in patients who were less functionally limited at baseline (NYHA 2 and 3) compared to BNP >100 or 6MWD. This finding further bolsters our assertion that HRR is an extremely important biomarker as a predictor of clinical worsening even among less symptomatic patients with PAH.

Abnormal HRR1 had a strong association with several indicators of poor prognosis that are well established in the PH literature. These include TCW, hospitalization for PH worsening, death, poor 6MWD, poor WHO FC, increased BNP, serum sodium ≤136, RV systolic dysfunction, and presence of pericardial effusion (1,2). However, HRR1 <16 was a better predictor of clinical worsening than any of these factors. We also analyzed predictors of HRR1 <16 and found that poor WHO FC, abnormal renal function, RV systolic dysfunction, and the presence of pericardial effusion were important predictors. These are all well known indicators of poor prognosis in patients with PAH (1,2).

It is recognized that increase in heart rate with exercise is a function of both sympathetic activation as well as parasympathetic withdrawal, however, recovery of heart rate during the initial resting period is a function of parasympathetic reactivation (29). Savin et al (30) initially postulated that sympathetic withdrawal contributes more to HRR soon after peak exercise, with parasympathetic activation playing a greater role later in recovery. Subsequent studies indicated a more important role for parasympathetic reactivation (31,32) implying that sympathetic activity withdrawal did not contribute significantly to initial HRR after exercise termination. Imai et al (29) examined the physiologic characteristics of HRR after exercise in healthy adults, athletes, and patients with chronic heart failure and found that early heart rate recovery was markedly prolonged by atropine administration in normal volunteers, indicating that it is mainly regulated by vagal reactivation. Recent studies have found evidence of autonomic dysfunction and sympathetic over-activation in patients with PAH (14). Similar to patients with chronic heart failure (33,34), sympathetic over-activity has also been

associated with survival in patients with PAH (12,13). The poor HRR may be a function of continued sympathetic activation and a lack of the normal parasympathetic re-activation at the end of the 6MW test (29). Patients with chronic heart failure have reduced tonic vagal activity (35,36) and although similar data is not available in patients with PAH, this remains a plausible hypothesis in this cohort and requires further study.

We did note that 8 of 12 patients on beta-blocker therapy for high blood pressure were in the poor HRR1 group indicating an increased level of sympathetic activity in this cohort. Previous studies, in patients undergoing evaluation for left-sided heart disease, have indicated that the use of beta-blockers had no significant impact on the prognostic value of HRR (15,31). The size of our cohort precludes assessment of the true impact of beta-blockade use in our patients, however, even after excluding patients on beta-blockers we found a very strong association between poor HRR and clinical worsening. We also analyzed our data after excluding patients in whom lung transplantation was the clinical worsening event because timing of lung transplantation may be affected by factors such as organ availability that are not related to PH worsening. This analysis still showed that HRR1 <16 was the best predictor of TCW.

There was a strong association between 6MWD and delta HR i.e. the further a patient walked, the greater the change in heart rate from baseline. There was also a strong association between HRR1 and 6MWD as well as peak HR and delta HR (Table 1 online supplement). Since HRR1 is an indicator of cardiovascular reserve, we postulate that patients with better cardiovascular function were able to walk further, increase their heart rate appropriately with exercise, and have a better HRR1 compared to patients with more significant cardiovascular limitation. It is interesting to note that, despite these

associations, HRR1 was a better predictor of clinical worsening compared to 6MWD, delta HR, or peak HR.

A limitation of the study is its retrospective nature. Patients included in the study did not undergo repeat right heart catheterization and we used historical right heart catheterization for our analysis. Most retrospective studies addressing clinical outcomes (such as hospitalization, six-minute walk, and survival) in patients with PAH (37-41) have used historical right heart catheterization data because many practitioners do not repeat right heart catheterization routinely in view of the invasive nature of the procedure. Studies that have performed right heart catheterization before and after initiation of PH specific therapy have shown that there is often only a slight improvement in the hemodynamic parameters (42). It is important to note that some baseline hemodynamic parameters were still predictive of clinical worsening in our cohort. This may reflect that the medications used to treat PH do not normalize pulmonary hemodynamics in most instances and baseline hemodynamics continue to be clinically relevant in the patient's long term outcomes. Regarding modeling for HRR after 6MWT, the time lag between the RHC and the 6MWT may have biased our analysis and this may be why baseline hemodynamic parameters were not significant predictors by multivariate modeling.

In summary, our study shows that HRR1 is an easily measured biomarker that is highly predictive of clinical worsening and TCW in patients with IPAH. Our results further show that the addition of HRR1 to 6MWD increases the capacity of 6MWD to predict clinical worsening and TCW in patients with IPAH. Further studies are needed to better characterize the utility of this biomarker in prospective studies and larger populations. Studies are also needed to define its clinical utility in other forms of PAH.

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Figure legends:

Figure 1: HRR1 has a strong positive correlation with 6MWD

Figure 2: K-M curve showing that patients with reduced HRR1 (<16 beats) had an increased propensity to have clinical worsening and had shorter time to clinical worsening compared to patients with HRR1 ≥16 beats

Figure 3: Analysis by c-index showed that HRR<16 improved the ability of 6MWD to predict time to clinical worsening (A) and the addition of other parameters did not increase this appreciably (B)

Table 1: Clinical characteristics of the study population

	Overall **N=75**	**HRR1 ≥ 16** **N=45 (60%)**	**HRR1 < 16** **N=30 (40%)**	
Factor	**N (%)** **Mean ± SD**	**N (%)** **Mean ± SD**	**N (%)** **Mean ± SD**	***P*-value**
Age (yrs.)	49±15	47± 13	53± 18	0.11
Female	59 (78.7)	37 (82)	22 (73)	0.36P
Caucasian	65 (87)	39 (87)	26 (87)	0.99P
BMI (kg/m^2)	29±8	30± 8	27± 6	0.11W
WHO FC, N (%)				<0.001C
I	9 (12)	9 (20)	0	
II	34 (45)	28 (62)	6 (20)	
III	24 (32)	8 (18)	16 (53)	
IV	8 (11)	0	8 (27)	
BUN (mg/dL)	16±7.6	14 ± 4.2	19.3 ± 10	0.009
Creatinine (mg/dL)	0.9±0.3	0.8 ± 0.2	1.1 ± 0.4	0.007
Sodium (mmol/L)	139±3	139 ± 2	139 ± 4	0.43
PFT parameters				
FVC (% pred)	81±17	86± 13	75± 20	0.023
FEV1 (% pred)	74±17	77± 14	70± 20	0.11
DLCO (% pred)	65±20	68± 17	62± 23	0.27
6MW test				
6MWD (m)	403±114	440±101	347±110	<0.001
6MWD (% pred)	71±17	76±13	63± 18	0.001
Nadir SpO2 (%)	91±5	91±5	90± 5	0.23
Baseline HR (b/min.)	84±14	84 ± 13	83± 15	0.73
Peak HR (b/min.)	122±22	129± 19	112± 23	<0.001

Delta HR (b/min.)	39±20	45±20	29 ± 17.5	<0.001
Suppl O2 (Yes)	27 (36)	13 (29)	14 (47)	0.12P
Beta blockers	12 (16)	4 (8.8)	8 (26.6)	0.050F
BNP (pg/ml)	177±290	47± 81	373± 373	<0.001
DE parameters				
RA enlargement	36 (49)	14 (31)	22 (73.3)	<0.001C
RVSP (mmHg)	81±29	73± 26	92± 31	0.007
RV dysfunction (mod or severe)	50 (67)	26 (58)	24 (80)	0.040P
Pericardial effusion present	18 (24)	6 (13)	12 (40)	0.008P
Baseline hemodynamics				
mRAP (mmHg)	10±6	8± 4	13 ± 6.5	<0.001
sPAP (mmHg)	85±19	81 ± 18.5	91 ± 19	0.030
dPAP (mmHg)	37±11	35± 8	40± 14	0.10
mPAP (mmHg)	52±13	48± 11	57± 15	0.010
CI (Fick) (ml/min/m^2)	2.5±0.9	2.6 ± 0.8	2.4± 1	0.41
MVO2 (%)	64±13	68±7	59± 18	0.090
TPG (mmHg)	35±13	35±10	36± 17	0.84
PVR (Woods units)	9±6	8±5	10±7	0.29W
PH medications at time of 6MWT				0.73
None	4	0	4	
PP	13	10	3	
Single Oral	11	8	3	
Combination (OP)	34	19	15	
Combination (other)	13	8	5	

Percentages by column groups.

All comparison by Students two sample T-test unless specified

W= Wilcoxon rank sum test; P= Pearson's chi-square test; C= Cochran-Armitage trend test; F= Fisher's exact test

HRR1: heart rate recovery after one minute of rest; BMI: body mass index; WHO FC: World Health Organization functional class; BUN: blood urea nitrogen; PFT: pulmonary function test; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; DLCO: diffusion capacity for carbon monoxide; 6MW: six minute walk; 6MWD: distance walked in 6 minutes; HR: heart rate; Delta HR: peak HR-baseline HR; Suppl O2: patients using supplemental oxygen during 6MWT; BNP: B-type natriuretic peptide; DE: Doppler echocardiography; RA: right atrium; RVSP: right ventricular systolic pressure; RV: right ventricle; mRAP: mean right atrial pressure ; sPAP: systolic pulmonary arterial pressure; dPAP: diastolic pulmonary arterial pressure; mPAP: mean pulmonary arterial pressure; CI: cardiac index; MVO2: mixed venous oxygen saturation; TPG: trans-pulmonary gradient; PVR: pulmonary vascular resistance; PP: parenteral prostanoid therapy; OP: combination of oral and parenteral agent

Table 2: Characteristics of 'worsening' events in the study population

Worsening Event	**Overall (N=75)**	**HRR ≥16 (N=45)**	**HRR <16 (N=30)**	***p*-value**
All events	24	6 (13)	18 (60)	<0.001
Death	10	3 (7)	7 (23)	0.07 F
Lung Transplant	6	2 (4)	4 (13)	0.21 F
Hospitalization for PH	9	3 (7)	6 (20)	0.14 F
Escalation of therapy	13	2 (4)	11 (37)	<0.001

Percentages by column groups

HRR: heart rate recovery; PH: pulmonary hypertension

Table 3. Uni-variable and multivariable Cox proportional hazard analysis for 'worsening' events

Univariable Analysis			
Factor	**HR**	**95% CI**	***P*-value**
HRR1 (<16 vs. ≥16)	7.21	(2.65, 19.63)	0.0001
6MWD (% Predicted)	0.94	(0.92, 0.97)	0.0001
mPAP (mmHg)	1.06	(1.03, 1.10)	0.0004
BNP (pg/ml)	1.002	(1.001, 1.003)	<0.001
mRAP (mmHg)	1.15	(1.08, 1.23)	<0.001
RVSP (mmHg)	1.02	(1.008, 1.03)	0.002
WHO FC (3+4 vs. 1+2)	3.57	(1.46, 8.70)	0.005
6MWD <332 meters (Yes vs. No)	3.36	(1.45, 7.80)	0.005
6MWD (meters)	0.99	(0.98, 0.99)	0.005
RVSD (mod+sev vs. abs+mild)	12.95	(1.73, 96.57)	0.01
FVC (% Predicted)	0.97	(0.94, 0.99)	0.02
BMI (kg/m^2)	0.90	(0.82, 0.99)	0.03
BUN (mg/dL)	1.03	(0.99, 1.07)	0.06
Creatinine (mg/dL)	3.06	(0.95, 9.84)	0.06
Multivariable Analysis			
Factor	**HR**	**95% CI**	***P*-value**
HRR1 (<16 vs. ≥16)	5.20	1.82-14.84	0.002

mPAP	1.04	1.007-1.08	0.02

BMI: body mass index; WHO FC: World Health Organization functional class; BUN: blood urea nitrogen; BNP: B-type natriuretic peptide; EF: ejection fraction; RVSP: right ventricular systolic pressure; RVSD: right ventricular systolic dysfunction; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second; DLCO: diffusion capacity for carbon monoxide; 6MWD: distance walked in six minutes; HRR1: heart rate recovery after one minute of rest; mRAP: mean right atrial pressure ; sPAP: systolic pulmonary arterial pressure; mPAP: mean pulmonary arterial pressure; CI: cardiac index; MVO2: mixed venous oxygen saturation; TPG: trans-pulmonary gradient; PVR: pulmonary vascular resistance; HR: heart rate; Delta HR: peak HR-baseline HR

Table 4: Utility of HRR <16 in predicting clinical worsening in patients by NYHA functional class

		NYHA 1	NYHA 2	NYHA 3	NYHA 4
Total (N)	75	9 (12%)	34 (45%)	24 (32%)	8 (11%)
N with worsening event	24	1 (4%)	6 (25%)	9 (37.5%)	8 (33%)
Among those with a worsening event	Those with 6MWD <335m	0	0	5 (55%)	8 (100%)
	Those with BNP >100 pg/ml	0	1 (17%)	6 (67%)	8 (100%)
	Those with HRR1 <16 b/m	0	3 (50%)	7 (78%)	8 (100%)

See Tables 1 and 3 legends for details

Table 5a: Logistic regression for AUC A) comparing HRR1 and 6MWD; B) assessing the additive value of HRR1 to 6MWD in predicting 'worsening'

A) Logistic regression model	Response	Predictor	C-statistic
1	Worsening	6MWD <380*	0.596
2	Worsening	6MWD <335**	0.653
3	Worsening	6MWD (m)	0.703
4	Worsening	HRR1	0.730
5	Worsening	HRR1 <16	0.757

B) Logistic regression model	Response	Predictor	C-statistic
1	Worsening	HRR1 + 6MWD (m)	0.729
2	Worsening	HRR1 <16 +6MWD <380	0.754
3	Worsening	HRR1 <16 + 6MWD <335	0.773

*6MWD cut-off shown to be best predictor of survival in patients with IPAH on therapy (ref 11)

** Best 6MWD cut-off that predicted worsening in our cohort by ROC analysis

6MWD: distance walked in 6 minutes; HRR1: heart rate recovery after one minute of rest; m: meters

Table 5b: Cox proportional regression for AUC A) comparing HRR1 and 6MWD; B) assessing the additive value of HRR1 to 6MWD in predicting 'time to worsening'

C) Cox proportional regression model	Response	Predictor	C-index
1	Time to worsening	6MWD <380*	0.6031
2	Time to worsening	6MWD <335**	0.6760
3	Time to worsening	6MWD (m)	0.6965
4	Time to worsening	HRR1	0.7224
5	Time to worsening	HRR1 <16	0.7308

D) Cox proportional regression model	Response	Predictor	C-index
1	Time to worsening	HRR1 + 6MWD (m)	0.6929
2	Time to worsening	HRR1 <16 +6MWD <380	0.7164
3	Time to worsening	HRR1 <16 + 6MWD <335	0.7499

See Table 5a legend for details

Table 6: Univariable and multivariable logistic regression analysis for predictors of HRR1 <16

Univariable Analysis			
Factor	**OR**	**95% CI**	***P*-value**
BNP (pg/ml)	1.0	(1.005, 1.01)	0.0003
6MWD <332 meters (Yes vs. No)	8.1	(2.7, 24.1)	0.0002
WHO FC (3+4 vs. 1+2)	18.5	(5.7, 60)	<0.001
6MWD (meters)	0.9	(0.9, 0.9)	0.001
mRAP (mmHg)	1.1	(1.06, 1.3)	0.002
Peak heart rate	0.9	(0.9, 0.9)	0.002
Delta heart rate	0.9	(0.9, 0.9)	0.002
6MWD (% predicted)	0.9	(0.9, 0.9)	0.002
6MWD <380 meters (Yes vs. No)	4.4	(1.6, 11.8)	0.003
Creatinine (mg/dL)	13.1	(2.1, 81.9)	0.006
RVSP (mmHg)	1.0	(1.007, 1.04)	0.008
BUN (mg/dL)	1.1	(1.03, 1.2)	0.009
Pericardial effusion (present vs. absent)	4.3	(1.4, 13.3)	0.010
mPAP (mmHg)	1.0	(1.01, 1.09)	0.010
Sodium ≤136 (mmol/L) (Yes vs. No)	5.0	(1.2, 21.1)	0.020
FVC % predicted	0.9	(0.9, 0.9)	0.020
sPAP (mmHg)	1.0	(1.002, 1.05)	0.030
RVSD (mod+sev vs. abs+mild)	2.9	(1.000, 8.543)	0.050

Multivariable Analysis			
Factor	**OR**	**95% CI**	***P*-value**
BNP (pg/ml)	1.009	1.003-1.01	0.005
WHO FC (3+4 vs. 1+2)	9.6	2.3-39.5	0.002

See Tables 1 and 3 legends for details

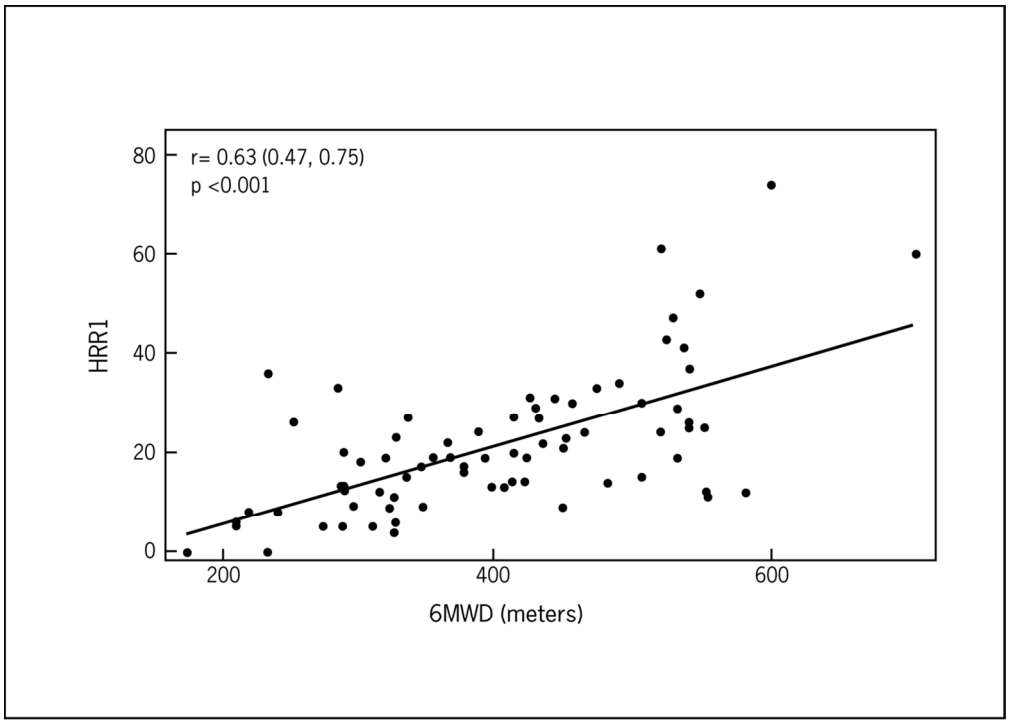
Table 7: Association between HRR1 <16 and several known predictors of poor prognosis in PAH

			Hrr1 < 16		Hrr1 ≥ 16			
Factor	**Level**	**Total**	**N**	**(%)**	**N**	**(%)**	**Odds Ratio (CI)**	***P*-value***
Any worsening event							9.7 (3.1, 30.1)	<0.001
	Yes	24	18	75	6	25		
	No	51	12	23.5	39	76.5		
Hospitalization for PH							3.5 (0.8, 15.2)	0.090
	Yes	9	6	67	3	33		
	No	66	24	36	42	64		
Escalation of Therapy							12.4 (2.5, 61.6)	0.002
	Yes	13	11	85	2	15		
	No	62	19	31	43	69		
Death							4.2 (1, 18)	0.040
	Yes	10	7	70	3	30		
	No	65	23	35	42	65		
6MWD <332 meters							8.1 (2.7, 24.1)	0.0002
	Yes	25	18	72	7	28		
	No	50	12	24	38	76		
6MWD <380 meters							4.4 (1.6, 11.8)	0.003
	Yes	34	20	59	14	41		
	No	41	10	24	31	76		
Use of supplemental O2 with 6MWT							2.1 (0.8, 5.6)	0.1
	Yes	27	14	52	13	48		
	No	48	16	33	32	67		
WHO FC							18.5 (5.7, 60)	<0.001
	WHO 3+4	32	24	75	8	25		
	WHO 1+2	43	6	14	37	86		
BNP >100 (pg/ml)							28 (7.468, 108.711)	<0.001
	Yes	25	21	84	4	16		

	No	45	7	16	38	84		
Sodium ≤136 (mmol/L)							5 (1.226, 21.135)	0.020
	Yes	11	8	73	3	27		
	No	64	22	34	42	66		
RV systolic dysfunction							2.9 (1.000, 8.543)	0.050
	Absent or mild	25	6	24	19	76		
	Moderate or severe	50	24	48	26	52		
BMI >30 (kg/m^2)							0.5 (0.210, 1.613)	0.30
	Yes	25	8	32	17	68		
	No	47	21	45	26	55		
Pericardial effusion							4.3 (1.403, 13.386)	0.010
	Present	18	12	67	6	33		
	Absent	57	18	32	39	68		

*P-values are from the logistic regression.

See Tables 1 and 3 legends for details



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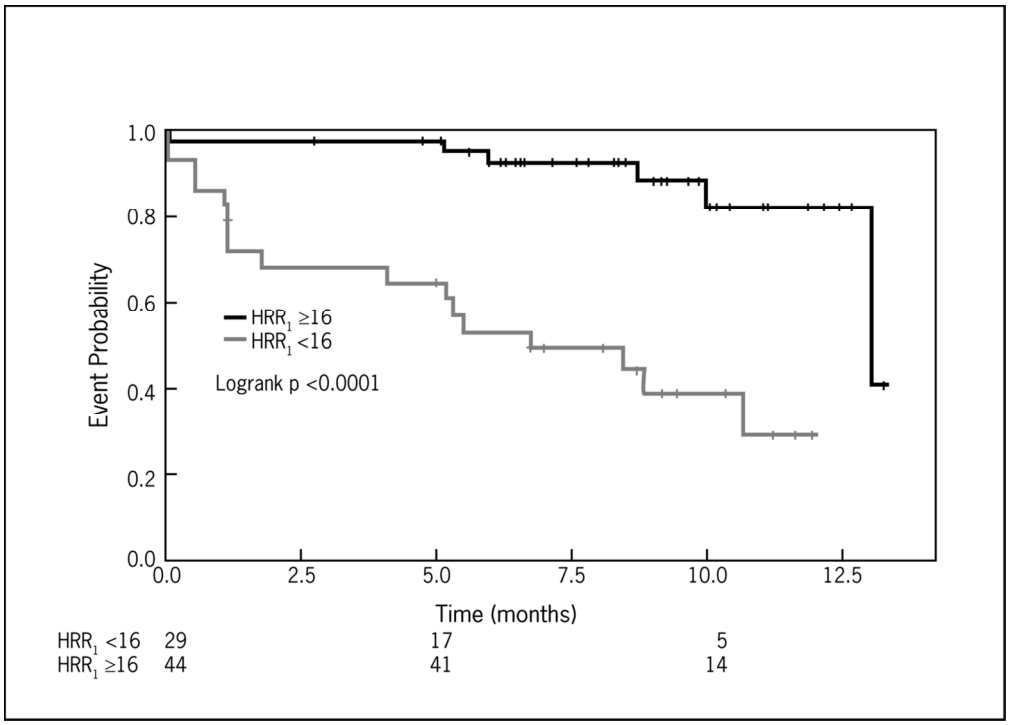

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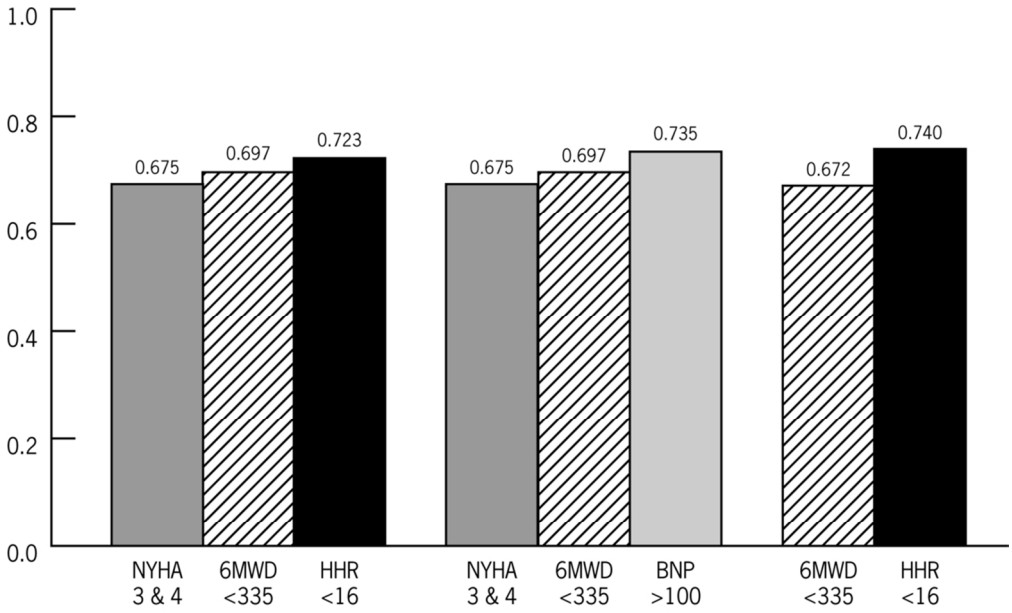

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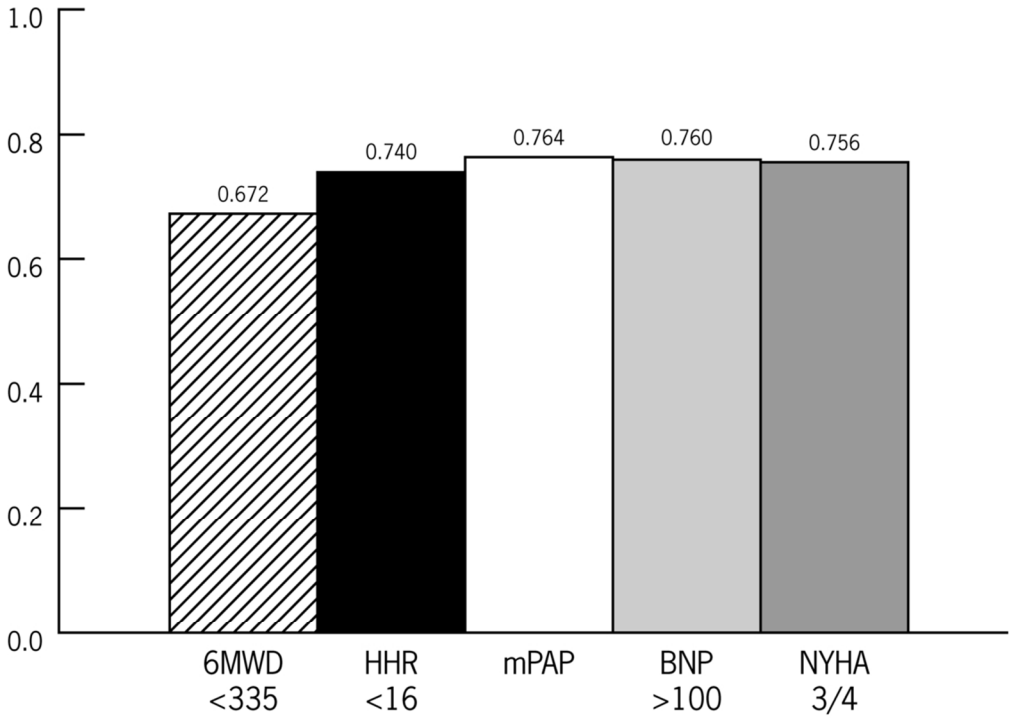

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